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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 7/06

A1

(11) International Publication Number: WO 87/ 00427

(43) International Publication Date: 29 January 1987 (29.01.87)

(21) International Application Number: PCT/US86/01393

(22) International Filing Date: 3 July 1986 (03.07.86)

(31) Priority Application Numbers: 757,131
858,050

(32) Priority Dates: 18 July 1985 (18.07.85)
30 April 1986 (30.04.86)

(33) Priority Country: US

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(81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BG, BR, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent).

Published
With international search report.

(54) Title: TOPICAL COMPOSITION AND METHOD FOR STIMULATING HAIR GROWTH

(57) Abstract

The composition contains, in an occlusive or semiocclusive pharmaceutical carrier, minoxidil, a hydroxyl radical scavenger such as DMSO, and optimally, an antiandrogen such as spironolactone. The method involves applying the composition to skin, preferably water-soaked skin, once a day. Also disclosed is a synergistic vehicle for topical hair growth stimulants such as minoxidil and 1,2,4-benzothiadiazine 1,1-dioxides. The vehicle contains an oil and water emulsion, a hydroxyl radical scavenger such as DMSO, and optimally, an antiandrogen such as spironolactone.

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APPLICATION FOR PATENT

TOPICAL COMPOSITION AND METHOD FOR STIMULATING HAIR GROWTH

SPECIFICATION

Field of the Invention

This invention relates to a composition and method for treating baldness, particularly androgenic alopecia.

Background of the Invention

Various treatments were available for conditions such as male and female pattern baldness and alopecia areata. Several substances were known to be effective when administered internally, but had undesirable concomitant systemic effects and the hypertrichosis was not confined to the scalp area. In an effort to avoid these side effects and to confine the hypertrichosis to the scalp area, several attempts were made to apply such substances in a topical preparation to the affected area. However, such attempts had generally been only marginally successful, and the results obtained with the topical preparation containing the orally effective substances were comparable to and generally little better than those obtained with topical application of the carrier only.

U.S. Patent 4,139,619 described a process for stimulating the growth of mammalian hair by the application of 6-amino-4-(substituted amino)-1,2-dihydro-1-hydroxy-2-iminopyrimidines to mammalian skin in association with a topical pharmaceutical carrier.

U.S. Patent 4,347,245 described a composition containing spironolactone in a liquid carrier such as alcohol, urea, mineral oil or white petrolatum.

Stewart, M.E. et al., "Antiandrogens and the Skin," International Journal of Dermatology, Vol. 17, pp. 167-179 (1978) described the application to the foreheads of acne patients of 10% cyproterone in 50% aqueous dimethyl sulfoxide, with no reduction in sebum secretion or improvement in acne being produced.

U.S. Patent 4,367,227 described a composition for reducing sebum secretion when applied to the skin, which composition contained cyproterone acetate dissolved in a C_2-C_3 aliphatic alcohol.

Summary of the Invention

The present invention is a composition for stimulating the growth of hair including, in a pharmaceutical carrier, (i) minoxidil or a homolog or analog thereof and (ii) dimethyl sulfoxide or a substantially equivalent hydroxyl radical scavenger in a synergistically effective amount. Optimally, the composition also includes an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

In another aspect, the invention is a method of stimulating the growth of hair by applying to the skin to be treated a composition including, in a pharmaceutical carrier, (i) minoxidil or a homolog or analog thereof and (ii) dimethyl sulfoxide or a substantially equivalent hydroxyl radical scavenger in a synergistically effective amount. Optimally, the composition applied also includes an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

In yet another aspect, the present invention provides a pharmaceutical vehicle for topical application of hair growth stimulants which functions as a synergist to improve the effectiveness of the hair growth stimulant. The vehicle consists essentially of an emulsion of oil and

water and substantially homogenously dispersed therein, a pharmaceutically acceptable hydroxyl radical scavenger in a proportion which is synergistically effective to simulate hair growth when a hair growth stimulant is dispersed in the vehicle. Optimally, the vehicle also includes an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

In still another aspect, the invention is an improvement in the method of stimulating the growth of hair by applying to the skin to be treated a composition including a hair growth stimulant in association with a pharmaceutical carrier. The improvement comprises providing a vehicle consisting essentially of an emulsion of oil and water and substantially homogenously dispersed therein a hydroxyl radical scavenger in a synergistically effective amount to stimulate hair growth. Optimally, the vehicle also includes an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

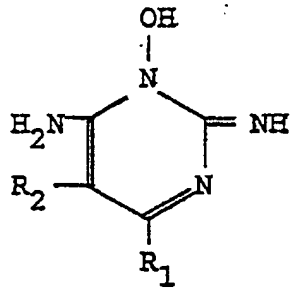
Detailed Description of the Invention

Briefly, the composition of the invention includes a pharmaceutical carrier, minoxidil or its equivalent, dimethyl sulfoxide (DMSO) or its equivalent, and optimally, an antiandrogen.

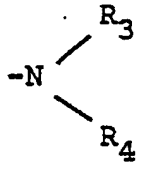
The carrier of the composition, in which the minoxidil, DMSO and any antiadrogen will generally be substantially homogenously dispersed, is preferably an occlusive or semi-occlusive preparation which may be a water-in-oil emulsion, but is most preferably an oil-in-water emulsion. As used herein, the terms "occlusive" or "semi-occlusive" are used in reference to a carrier which substantially prevents or inhibits, respectively, evaporation of water from the skin to which it is applied. Suitable water-in-oil emulsions are commercially available under the designations Aquaphor, cold cream, Eucerin, hydrous lanolin, Hydrosorb, hydrophilic petrolatum, Nivea, Polysorb, Qualatum and Velvachol. Suitable oil-in-water emulsions are available

commercially under the designations acid mantle cream, Almay emulsion cream, Cetaphil, Dermabase, Dermovan, hydrophilic ointment, Keri cream, Lubriderm cream, Multibase cream, Neobase cream, Univase cream, Vanibase cream, and Wibi. The carrier may further contain various other emollients, emulsifiers, water, perfumes, colorants, preservatives and the like. In a preferred embodiment, the carrier comprises the Dermovan emulsion, propylene glycol and water.

Minoxidil is 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine and also includes tautomers such as 2,4-diamino-6-piperidinopyrimidine 3-oxide. Contemplated as suitable substitutes for minoxidil in the composition are the other free base forms and acid addition salts of the 6-amino-4-(substituted amino)-1,2-dihydro-1-hydroxy-2-iminopyrimidines described in U.S. Patent 3,461,461 which is incorporated herein by reference. Briefly, such compounds include 1,2-dihyro-1-hydroxypyrimidines of the formula:



wherein R_1 is a moiety selected from the group consisting of moieties of the formula:



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together, R_3 and R_4 may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino,

morpholino and 4-lower-alkyl-piperazinyl, each of the hetrocyclic moieties having attached as substituents on the carbon atoms thereof 0-3 lower alkyl groups, hydroxy or alkoxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkoxyaralkyl, and lower haloaralkyl and the tautomers and pharmacologically acceptable acid addition salts thereof. These compounds and their preparation are also described in U.S. Patents 3,382,247 and 3,644,364.

The minoxidil or suitable substitute therefor is preferably present in the composition in an amount of from about 0.1 to about 20 percent by weight of the composition, more preferably from about 0.5 to about 3 percent by weight, and most preferably about 2 percent by weight. For convenience, reference is made hereinbelow to minoxidil, but it is to be understood that the suitable substitutes therefor described above may be present partially or entirely in lieu of minoxidil itself.

The second essential ingredient is DMSO or a substantially equivalent hydroxyl radical scavenger in a synergistically effective amount. Hydroxyl radical scavengers are, for example, sulfoxides, purines, pyrimidines, thiols, alcohols, halide ions, aromatic hydrocarbons and the like. Hydroxyl radical scavengers suitable in the composition of the present invention are those pharmaceutically acceptable hydroxyl radical scavengers which have a hydroxyl radical scavenger effectiveness substantially equivalent to or better than DMSO. Preferred hydroxyl radical scavengers are the alkyl methyl sulfoxides in which the alkyl substituent has from one to about 14 carbon atoms and the β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from two to about 14 carbon atoms, with dimethyl sulfoxide being particularly preferred. Specific representative examples of such sulfoxides include, in addition to DMSO,

hexyl methyl sulfoxide, decyl methyl sulfoxide, dodecyl methyl sulfoxide, tetradecyl methyl sulfoxide, β-hydroxydecyl methyl sulfoxide, β-hydroxydodecyl methyl sulfoxide, β-hydroxytetradecyl methyl sulfoxide, and the like. For convenience, reference is made hereinbelow to DMSO, but it is to be understood that other suitable hydroxyl radical scavengers may be present, partially or entirely, in lieu of DMSO.

The hydroxyl radical scavenger is present in the composition in a proportion effective to, synergistically with the minoxidil, stimulate the growth of hair. For the sulfoxides such as DMSO, this amount is generally from about 5 to about 25 percent by weight of the composition, preferably about 15-20 percent by weight. Depending on the particular carrier, the amount of DMSO present may be adjusted to avoid phase separation.

It has also been found that the hair growth stimulation effected by the present composition is improved when an antiandrogen which interferes with the binding of dihydrotestosterone to receptors in hair follicles is present. These compounds function primarily to block dihydrotestosterone receptors rather than to inhibit the reduction of testosterone. Exemplary of such antiandrogens are spironolactone, cyproterone, cyproterone acetate, and the like.

Effective amounts of the antiandrogen generally range from about 0.01 to about 5 percent by weight of the composition, but more or less than this may be used depending on the particular antiandrogen. The optimum amount is about 0.01 percent by weight of the composition for spironolactone, about 0.1 percent for cyproterone, and about 0.1 percent for cyproterone acetate. Quite surprisingly, at amounts above these optimums, the effect of the antiandrogens is not as great, and for unknown reasons, in some cases the presence of the antiandrogen in the composition in amounts in substantial excess of the optimum results in a reduced effectiveness in stimulating

hair growth in comparison to the composition containing no antiandrogen.

According to the method of the invention, the composition of the invention described above is applied topically to the skin to be treated, such as the scalp. Preferably, the application is once a day with a sufficient amount of the composition to cover the area at which the stimulation of hair growth is desired. It has been found that results are improved when the composition is applied after water-soaking the skin. Thus, a preferred embodiment of the method is convenient in that the composition can be applied once daily immediately following bathing.

Generally, best results are obtained in treatment of bald or thinly-haired scalp areas in which hair loss has not occurred for a period of time substantially in excess of about 3-5 years. The effectiveness also depends, although to a lesser degree, inversely on the age of the user.

Quite surprisingly, it has been discovered that the presence of DMSO in the minoxidil-containing topically applied pharmaceutical preparation of this invention results in a marked enhancement in the treatment of balding in contrast to the heretofore known minoxidil-containing topical pharmaceutical preparations. While DMSO has been present in topically applied prior art preparations to improve percutaneous penetration of pharmacologically active substances other than minoxidil, the concentration of DMSO in water must be above about 50 percent by weight before any improvement in penetration is obtained. Because DMSO is effective to produce hypertrichosis when present in the minoxidil-containing composition of this invention at concentrations much less than 50 percent by weight, although not presently fully understood, it is believed that its synergistic effect is due to a pharmacological effect of DMSO, such as, for example, its property as a potent hydroxyl radical

scavenger, rather than any effect on increased absorption of minoxidil by the skin. This belief is also supported by studies which have reported systemic side effects produced by topical applications of prior art preparations containing 5 weight percent minoxidil, with only marginally, if any, better results in the stimulation of hair growth in comparison to the topical application of preparations containing minoxidil at 1 percent by weight, thereby indicating that absorption of minoxidil by the skin was adequate. See, for example, Headington, J.R. et al., "Clinical and Histological Studies of Male Pattern Baldness Treated with Topical Minoxidil," Current Therapeutic Research, Vol. 36, pp. 1098-1105 (1984). It is to be understood, however, that the present invention is not intended to be limited by theory.

It is also quite surprising that the presence of DMSO in the present composition generally results neither in irritation of the skin to which the composition is applied (in about 99 percent of patients) nor in an unpleasant odor or taste being experienced, in sharp contrast to heretofore known DMSO-containing preparations.

Application of the composition of this invention to the bald or thinly-haired scalp has been observed to be effective to substantially restore the normal growth of hair in about 3-6 months in about 90 percent of patients treated who had a history of hair loss of less than 5 years. The treatment is substantially free of systemic side effects and the hypertrichosis is confined to the area of application.

In about 1 percent of patients treated, there is some local allergenic dermatitis, which compares to the reported incidence of about 1 percent for local allergic reaction to minoxidil itself when topically applied in an alcohol-based vehicle. See, for example, Tkach, R.J. "Side-Effects of Topical Minoxidil Treatment of Alopecias," Dermatological Allergy, Vol. 6, p. 42 (1983). However, in sharp contrast to the heretofore known topical

minoxidil preparations, it has been found, quite surprisingly, that the patients which exhibit a local allergic reaction to the present composition can be treated for a period of time, preferably about 2-3 months, with minoxidil in an alcohol-based carrier, and can thereafter be treated with the composition of this invention without experiencing any dermatitis. It is believed that the dermatitis in patients treated with the present composition is due to allergic reaction to the DMSO and/or carrier, which can be avoided by conditioning with minoxidil in the alcohol-based carrier. It is further believed that those patients who would experience an allergic reaction to minoxidil in other preparations do not do so when the present composition is employed.

Briefly, the vehicle of the invention includes a water and oil emulsion, a hydroxyl radical scavenger, and optimally, an antiandrogen.

The emulsion in which the hair growth stimulant, hydroxyl radical scavenger and any antiadrogen will generally be substantially homogenously dispersed, is preferably an occlusive or semi-occlusive preparation which may be a water-in-oil emulsion, but is most preferably an oil-in-water emulsion. Suitable water-in-oil emulsions are commercially available under the designations Aquaphor, cold cream, Eucerin, hydrous lanolin, Hydrosorb, hydrophilic petrolatum, Nivea, Polysorb, Qualatum and Velvachol. Suitable oil-in-water emulsions are available commercially under the designations acid mantle cream, Almay emulsion cream, Cetaphil, Dermabase, Dermovan, hydrophilic ointment, Keri cream, Lubriderm cream, Multibase cream, Neobase cream, Univase cream, Vanibase cream, and Wibi. The emulsion may further contain various other emollients, emulsifiers, perfumes, colorants, preservatives and the like. In a preferred embodiment, the emulsion comprises the Dermovan emulsion, propylene glycol and water.

The second essential ingredient of the vehicle is DMSO or a substantially equivalent hydroxyl radical scavenger in a synergistically effective amount. Hydroxyl radical scavengers are, for example, sulfoxides, purines, pyrimidines, thiols, alcohols, halide ions, aromatic hydrocarbons and the like. Hydroxyl radical scavengers suitable in the carrier of the present invention are those pharmaceutically acceptable hydroxyl radical scavengers which have a hydroxyl radical scavenger effectiveness substantially equivalent to or better than DMSO. Preferred hydroxyl radical scavengers are the alkyl methyl sulfoxides in which the alkyl substituent has from one to about 14 carbon atoms and the β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from two to about 14 carbon atoms, with dimethyl sulfoxide being particularly preferred. Specific representative examples of such sulfoxides include, in addition to DMSO, hexyl methyl sulfoxide, decyl methyl sulfoxide, dodecyl methyl sulfoxide, tetradecyl methyl sulfoxide, β-hydroxydecyl methyl sulfoxide, β-hydroxydodecyl methyl sulfoxide, β-hydroxytetradecyl methyl sulfoxide, and the like. For convenience, reference is made hereinbelow to DMSO, but it is to be understood that other suitable hydroxyl radical scavengers may be present, partially or entirely, in lieu of DMSO.

The hydroxyl radical scavenger is present in the vehicle in a proportion effective to, synergistically with a hair growth stimulant such as minoxidil, stimulate the growth of hair. Preferably, the proportion of the hydroxyl radical scavenger is synergistically effective to stimulate the growth of hair when minoxidil is dispersed in the vehicle in a proportion of 2 percent by weight. For the sulfoxides such as DMSO, the synergistic amount is generally from about 5 to about 25 percent by weight of the vehicle, preferably about 15-20 percent by weight. Depending on the particular emulsion, the amount of DMSO present may be adjusted to avoid phase separation.

It has also been found that the hair growth stimulant synergism effected by the present vehicle is improved when an antiandrogen which interferes with the binding of dihydrotestosterone to receptors in hair follicles is present in the vehicle. These compounds function primarily to block dihydrotestosterone receptors rather than to inhibit the reduction of testosterone. Exemplary of such antiandrogens are spironolactone, cyproterone, cyproterone acetate, and the like.

Effective amounts of the antiandrogen generally range from about 0.01 to about 5 percent by weight of the vehicle, but more or less than this may be used depending on the particular antiandrogen. The optimum amount is about 0.2 percent by weight of the vehicle for spironolactone, about 0.1 percent for cyproterone, and about 0.1 percent for cyproterone acetate. Quite surprisingly, at amounts above these optimums, the effect of the antiandrogens is not as great, and for unknown reasons, in some cases the presence of the antiandrogen in the carrier in amounts in substantial excess of the optimum results in a reduced synergistic effectiveness in stimulating hair growth in comparison to the vehicle containing no antiandrogen.

The vehicle of the present invention has synergistic utility in the topical application of hair growth stimulants such as minoxidil. Generally, the minoxidil or other suitable hair growth stimulant will be substantially homogenously dispersed in the vehicle in an effective amount.

Minoxidil is 6-amino-1,2-dihydro-1-hydroxy-2-imino-4-piperidinopyrimidine and also includes tautomers such as 2,4-diamino-6-piperidinopyrimidine 3-oxide. Contemplated as suitable substitutes for minoxidil are the other free base forms and acid addition salts of the 6-amino-4-(substituted amino)-1,2-dihydro-1-hydroxy-2-iminopyrimidines described above.

Also contemplated as suitable substitutes for minoxidil are the 1,2,4-benzothiadiazine 1,1-dioxides (such as diazoxide) described in U.S. Patents 4,184,039 and 2,986,573 which are hereby incorporated herein by reference; 5,5-diphenyl-2,4-imidazolidinedione (dyphenylhydantoin) and related compounds described in U.S. Patent 2,409,754 which is hereby incorported herein by reference; and the porphyrins.

It is believed that other pharmacologically acceptable substances which form stable free radicals may also be hair growth stimulants suitably substituted for minoxidil. Free radicals are generally short-lived reactive chemical species having one or more electrons with unpaired spins. However, stable radicals can be formed in some species due to steric protection, resonance stabilization and other means of protecting the unpaired electron.

The minoxidil or suitable substitute therefor is preferably present in the vehicle in an amount of from about 0.1 to about 20 percent by weight of the vehicle, more preferably from about 0.5 to about 3 percent by weight, and most preferably about 2 percent by weight. For convenience, reference is made hereinbelow to minoxidil, but it is to be understood that the suitable substitutes therefor described above may be present partially or entirely in lieu of minoxidil itself.

According to the improved method of the invention, the vehicle of the invention described above having the hair growth stimulant dispersed therein is applied topically to the skin to be treated, such as the scalp. Preferably, the application is once a day with a sufficient amount of the hair growth stimulant-containing vehicle to cover the area at which the stimulation of hair growth is desired. It has been found that results are improved when the preparation is applied after water-soaking the skin. Thus, a preferred embodiment of

the method is convenient in that the preparation can be applied once daily immediately following bathing.

Generally, best results are obtained in treatment of bald or thinly-haired scalp areas in which hair loss has not occurred for a period of time substantially in excess of about 3-5 years. The effectiveness also depends, although to a lesser degree, inversely on the age of the user.

Quite surprisingly, it has been discovered that the presence of DMSO in the minoxidil-containing topically applied pharmaceutical preparation of this invention results in a marked enhancement in the treatment of balding in contrast to the heretofore known minoxidil-containing topical pharmaceutical preparations. While DMSO has been present in topically applied prior art preparations to improve percutaneous penetration of pharmacologically active substances other than minoxidil, the concentration of DMSO in water must be above about 50 percent by weight before any improvement in penetration is obtained. Because DMSO is effective to produce hypertrichosis when present in the minoxidil-containing preparation of this invention at concentrations much less than 50 percent by weight, although not presently fully understood, it is believed that its synergistic effect is due to a pharmacological effect of DMSO, such as, for example, its property as a potent hydroxyl radical scavenger, rather than any effect on increased absorption of minoxidil by the skin. This belief is also supported by studies which have reported systemic side effects produced by topical applications of prior art preparations containing 5 weight percent minoxidil, with only marginally, if any, better results in the stimulation of hair growth in comparison to the topical application of preparations containing minoxidil at 1 percent by weight, thereby indicating that absorption of minoxidil by the skin was adequate. See, for example, Headington, J.R. et al., "Clinical and Histological Studies of Male Pattern

Baldness Treated with Topical Minoxidil," Current Therapeutic Research, Vol. 36, pp. 1098-1105 (1984). It is to be understood, however, that the present invention is not intended to be limited by theory.

It is also quite surprising that the presence of DMSO in the present vehicle generally results neither in irritation of the skin to which the vehicle is applied (in about 99 percent of patients) nor in an unpleasant odor or taste being experienced, in sharp contrast to heretofore known DMSO-containing preparations.

Application of the vehicle of this invention having minoxidil dispersed therein to the bald or thinly-haired scalp has been observed to be effective to substantially restore the normal growth of hair in about 3-6 months in about 90 percent of patients treated who had a history of hair loss of less than 5 years. The treatment is substantially free of systemic side effects and the hypertrichosis is confined to the area of application.

In about 1 percent of patients treated, there is some local allergenic dermatitis, which compares to the reported incidence of about 1 percent for local allergic reaction to minoxidil itself when topically applied in an alcohol-based vehicle. See, for example, Tkach, R.J. "Side-Effects of Topical Minoxidil Treatment of Alopecias," Dermatological Allergy, Vol. 6, p. 42 (1983). However, in sharp contrast to the heretofore known topical minoxidil preparations, it has been found, quite surprisingly, that the patients which exhibit a local allergic reaction to the present minoxidil-containing preparation can be treated for a period of time, preferably about 2-3 months, with minoxidil in an alcohol-based carrier, and can thereafter be treated with minoxidil in the vehicle of this invention without experiencing any dermatitis. It is believed that the dermatitis in patients treated with the present vehicle is due to allergic reaction to the DMSO and/or emulsion, which can be avoided by conditioning with minoxidil in the

alcohol-based carrier. It is further believed that those patients who would experience an allergic reaction to minoxidil in other preparations do not do so when the present vehicle is employed.

The preparation and use of the present invention is illustrated by way of the following examples.

Example 1A -- Preparation of the Composition

A composition according to the invention was prepared with the ingredients and proportions listed in Table I-A.

Table I-A

Ingredient	Proportion
Dermovan emulsion[1]	15 pounds
DMSO	3 pints
Water	2 pints
Propylene glycol	2 pints
Minoxidil[2]	2 wt.%

Notes for Table I-A:

1. Obtained from Owen Laboratories; Dermovan emulsion contains water, glycerol stearate, glycerin, mineral oil, synthetic spermaceti, cetyl alcohol, butylparaben, propylparaben and methylparaben.
2. Obtained from The Upjohn Company under the designation Loniten.

The water and propylene glycol were added to the dry minoxidil in a suitable container. The DMSO was then added and the mixture was thoroughly mixed and allowed to stand overnight. Then, with constant stirring the Dermovan emulsion was added slowly. The mixture was then allowed to stand at least 24 hours with occasional stirring.

Examples 1B - 1D

Other compositions according to the invention were prepared with the ingredients and proportions listed in Tables I-B through I-D, respectively referred to hereinbelow as Examples 1B-1D. The compositions were prepared as in Example 1A with any spironolactone being added with the minoxidil.

Table I-B

Ingredient	Proportion
Dermovan emulsion[1]	15 pounds
DMSO	3 pints
Water	2 pints
Propylene glycol	2 pints
Minoxidil[2]	2 wt.%
Spironolactone	0.01 wt.%

Notes for Table I-B:

1. See Table I-A, note 1.
2. See Table I-A, note 2.

Table I-C

Ingredient	Proportion
Dermovan emulsion[1]	15 pounds
DMSO	3 pints
Water	2 pints
Propylene glycol	2 pints
Minoxidil[2]	1 wt.%
Spironolactone	0.01 wt.%

Notes for Table I-C:

1. See Table I-A, note 1.
2. See Table I-A, note 2.

Table I-D

Ingredient	Proportion
Dermovan emulsion[1]	15 pounds
DMSO	1 pint
Water	2 pints
Propylene glycol	2 pints
Minoxidil[2]	2 wt.%
Spironolactone	0.01 wt.%

Notes f r Table I-D:

1. See Table I-A, note 1.
2. See Table I-A, note 2.

Example 2A -- Use of the Composition

The composition prepared according to the procedure of Example 1A was used to treat the balding scalp area of a 27-year-old male patient with 9 years of hair loss, most of which had occurred during the 4 years preceding treatment. The patient had recently been treated in a formal clinical trial conducted by The Upjohn Company with topical minoxidil, believed to be 2 wt.% minoxidil in a solution of water (70 vol. %), ethanol (15 vol. %) and propylene glycol (15 vol. %), applied to the scalp three times a day for over a year with no effect. The composition of Example 1A was applied once a day to the water-soaked scalp, e.g. immediately following bathing, at a rate of about 0.5 ml per day. Visually perceptible hair growth at the previously bald areas of the scalp was observed after about 2 months of treatment. Nearly normal hair growth was observed at about 4-6 months of treatment.

Example 2B

The composition of Examples 1A, 1B and 1C were used to treat the balding scalp area of a 34-year-old male with 3-4 years of hair loss. The patient had previously been treated with topical minoxidil in the water/ethanol/propylene glycol solution described in Example 2A, with no substantial results. The composition of Example 1A was applied to the scalp as in Example 2A for about 3 months, then the composition of Example 1B for about 1 month, and thereafter the composition of Example 1C. The patient responded with visibly improved hair growth at about 2 months of treatment which continued to improve at six months.

Example 2C

The composition of Example 1A was used to treat the balding scalp area of a 26-year-old male with about 4 years of hair loss. The patient had previously been treated with topical minoxidil in the water/ethanol/propylene glycol solution as described in Example 2A, with no substantial results. The composition

of Example 1A was applied to the scalp as in Example 2A. By one month, the patient's hair line recession had stopped and there was a marked decrease in hair loss. At about 3 months, visibly improved hair growth was observed with forward movement of the hair line. Improvement in hair growth has continued.

Example 2D

The composition of Examples 1A and 1D were used to treat the balding scalp area of a 42-year-old male with about 12 years of hair loss. The patient had previously been treated with topical minoxidil in the water/ethanol/propylene glycol solution described in Example 2A, with no substantial results. The composition of Example 1A was applied to the scalp as in Example 2A for about 4 months, and thereafter the composition of Example 1C. The patient showed visibly improved hair growth beginning at two months of treatment, which continued.

Example 2E

The composition of Example 1C was used to treat the balding scalp area of a 26-year-old male with 1 year of hair loss. The patient had previously been treated with topical minoxidil in the water/ethanol/propylene glycol solution described in Example 2A, with no substantial results. The composition of Example 1C was applied to the scalp as in Example 2A. The patient showed decreased hair loss at one month with gradual replacement and marked forward progression of the hairline at four months, which has continued.

Example 2F

The composition of Example 1A was used to treat the balding scalp area of a 33-year-old male with about 5 years of hair loss. The patient had been previously treated with topical minoxidil in the Upjohn clinical trial as described in Example 2A with no substantial results. The composition of Example 1A was applied to the scalp as in Example 2A. Improved hair growth was visible

at two months and markedly so at three months. Improvement in hair growth has continued.

Example 2G

The composition of Examples 1A, 1B and 1C were used to treat the balding scalp area of a 34-year-old female with about 3-1/2 years of hair loss secondary to alopecia areata. The patient had previously been treated with topical therapy using chlorodinitrobenzene sensitization, with no substantial results. The composition of Example 1A was applied to the scalp as in Example 2A for about 4 months, then Example 1B for about 1 month, and Example 1C thereafter. The patient showed significantly decreased hair loss and improved growth of hair at two months. White hair was thickened and darkened with visible results present by three months. Progress has continued.

Example 2H

A 27-year-old male patient with about 5 years of hair loss from the scalp experienced local allergic dermatitis about 3 months after initial application of the composition of Example 1A to the scalp as in Example 2A. The application of this composition was discontinued, and topical application of 2 wt.% minoxidil in an alcohol-based carrier (70 vol.% water, 15 vol.% ethanol, 15 vol.% propylene glycol) was started without any allergic reaction. After about 2 months, application of the minoxidil in the alcohol-based carrier was discontinued, and application of the composition of Example 1A started. Throughout treatment, there was no allergic reaction to either the minoxidil in the alcohol-based carrier, or to the composition of Example 1A following sensitization with the minoxidil in the alcohol-based carrier. Improved hair growth was observed at about 2 months following initial application of minoxidil, and has continued.

In the patients treated thus far according to the invention, it has generally been observed that better results are obtained, i.e., a faster rate of hair growth

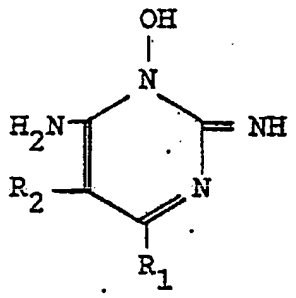
and an earlier appearance thereof, with the composition of Example 1B than are obtained with the compositions of Examples 1D, 1C and 1A, in decreasing order of relative effectiveness.

While I have described my invention above, many variations in the ingredients, proportions, and manner of preparation will occur to those skilled in the art. It is intended that all such variations which fall within the scope and spirit of the appended claims be embraced thereby.

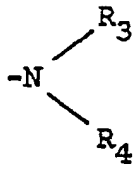
CLAIMS:

1. A composition for topical application to the skin to stimulate hair growth, comprising:

(a) from about 0.1 to about 20 weight percent of a 1,2-dihydro-1-hydroxypyrimidine compound selected from the group consisting of compounds of the formula:



wherein R_1 is a moiety selected from the group consisting of moieties of the formula:



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together, R_3 and R_4 may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino and 4-lower-alkyl-piperazinyl, each of said hetrocyclic moieties having attached as substituents on the carbon atoms thereof 0-3 lower alkyl groups, hydroxy or alkoxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkoxyaralkyl, and lower haloaralkyl, and the tautomers and pharmacologically acceptable acid addition salts thereof;

(b) a synergistically effective proportion of a pharmaceutically acceptable hydroxyl radical scavenger; and

(c) a pharmaceutical carrier in which said 1,2-dihydro-1-hydroxypyrimidine compound and said hydroxyl radical scavenger are substantially homogenously dispersed.

2. The composition of claim 1, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is minoxidil.

3. The composition of claim 1, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is present in an amount of from about 0.5 to about 3 percent by weight of the composition.

4. The composition of claim 1, wherein said hydroxyl radical scavenger is selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from one to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from two to about 14 carbon atoms and combinations thereof.

5. The composition of claim 4, wherein said hyroxyl radical scavenger is present in an amount of from about 5 to about 25 percent by weight of the composition.

6. The composition of claim 1, further comprising an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

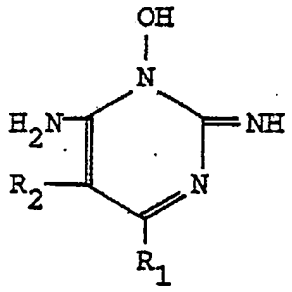
7. The composition of claim 6, wherein said antiandrogen is selected from the group consisting of: spironolactone, cyproterone, cyproterone acetate, and combinations thereof.

8. The composition of claim 6, wherein said antiandrogen is present in an amount of from about 0.01 to about 5 percent by weight of the composition.

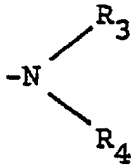
9. The composition of claim 1, wherein said carrier is an occlusive or semiocclusive carrier selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions.

10. A composition for topical application to the skin to stimulate hair growth, comprising:

(a) from about 0.5 to about 3 weight percent of a 1,2-dihydro-1-hydroxypyrimidine compound selected from the group consisting of compounds of the formula:



wherein R_1 is a moiety selected from the group consisting of moieties of the formula:



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together, R_3 and R_4 may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino and 4-lower-alkyl-piperazinyl, each of said hetrocyclic moieties having attached as substituents on

the carbon atoms thereof 0-3 lower alkyl groups, hydroxy or alkoxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkoxyaralkyl, and lower haloaralkyl, and the tautomers and pharmacologically acceptable acid addition salts thereof;

(b) from about 5 to about 25 percent by weight of a hydroxyl radical scavenger selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from one to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from two to about 14 carbon atoms, and combinations thereof; and

(c) an occlusive or semiocclusive pharmaceutical carrier in which said 1,2-dihydro-1-hydroxypyrimidine compound and said hydroxyl radical scavenger are substantially homogenously dispersed, said carrier selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions.

11. The composition of claim 10, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is minoxidil.

12. The composition of claim 10, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is present in an amount of about 2 percent by weight of the composition.

13. The composition of claim 10, wherein said hydroxyl radical scavenger is present in an amount of from about 15 to about 20 percent by weight of the composition.

14. The composition of claim 10, wherein said hydroxyl radical scavenger is dimethyl sulfoxide.

15. The composition of claim 10, further comprising from about 0.01 to about 5 percent by weight of an antiandrogen selected from the group consisting of: spironolactone, cyproterone, and cyproterone acetate.

16. The composition of claim 15, wherein said antiandrogen is spironolactone.

17. The composition of claim 16, wherein said spironolactone is present in an amount of about 0.01 percent by weight.

18. The composition of claim 15, wherein said antiandrogen is cyproterone.

19. The composition of claim 18, wherein said cyproterone is present in an amount of about 0.1 percent by weight.

20. The composition of claim 15, wherein said antiandrogen is cyproterone acetate.

21. The composition of claim 20, wherein said cyproterone acetate is present in an amount of about 0.1 percent by weight.

22. A composition for topical application to the skin to stimulate hair growth, comprising:

(a) about 2 percent by weight of minoxidil;

(b) from about 15 to about 20 percent by weight of dimethyl sulfoxide; and

(c) an occlusive or semiocclusive pharmaceutical carrier in which said minoxidil and said methyl sulfoxide are substantially homogenously dispersed, said carrier being an oil-in-water emulsion.

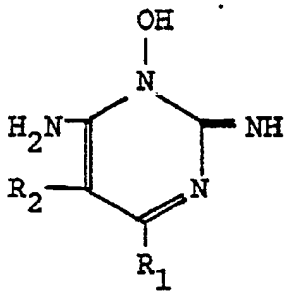
23. The composition of claim 21, further comprising:

(d) about 0.01 weight percent spironolactone substantially homogenously dispersed in said carrier.

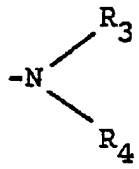
24. A method of stimulating hair growth, comprising:

applying to the skin a composition comprising:

(a) from about 0.1 to about 20 weight percent of a 1,2-dihydro-1-hydroxypyrimidine compound selected from the group consisting of compounds of the formula:



wherein R_1 is a moiety selected from the group consisting of moieties of the formula:



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together, R_3 and R_4 may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino and 4-lower-alkyl-piperazinyl, each of said hetrocyclic moieties having attached as substituents on the carbon atoms thereof 0-3 lower alkyl groups, hydroxy or alkoxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkoxyaralkyl, and lower haloaralkyl,

and the tautomers and pharmacologically acceptable acid addition salts thereof;

(b) a synergistically effective proportion of a pharmaceutically acceptable hydroxyl radical scavenger; and

(c) a pharmaceutical carrier in which said 1,2-dihydro-1-hydroxypyrimidine compound and said hydroxyl radical scavenger are substantially homogenously dispersed.

25. The method of claim 24, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is minoxidil.

26. The method of claim 24, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is present in an amount of from about 0.5 to about 3 percent by weight of the composition.

27. The method of claim 24, wherein said hydroxyl radical scavenger is selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from one to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from two to about 14 carbon atoms, and combinations thereof.

28. The method of claim 27, wherein said hyroxyl radical scavenger is present in an amount of from about 5 to about 25 percent by weight of the composition.

29. The method of claim 24, wherein said composition further comprises an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

30. The method of claim 29, wherein said antiandrogen is selected from the group consisting of: spironolactone, cyproterone, and cyproterone acetate.

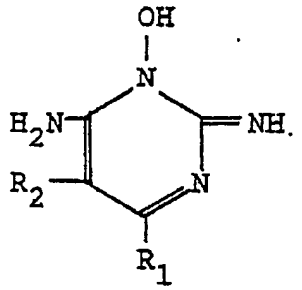
31. The method of claim 29, wherein said antiandrogen is present in an amount of from about 0.01 to about 5 percent by weight of the composition.

32. The method of claim 24, wherein said carrier is an occlusive or semiocclusive carrier selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions.

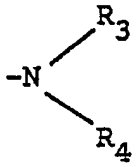
33. A method of stimulating hair growth, comprising:

applying to the skin a composition comprising:

(a) from about 0.5 to about 3 weight percent of a 1,2-dihydro-1-hydroxypyrimidine compound selected from the group consisting of compounds of the formula:



wherein R_1 is a moiety selected from the group consisting of moieties of the formula:



wherein R_3 and R_4 are selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower aralkyl, and lower cycloalkyl, and taken together, R_3 and R_4 may be a heterocyclic moiety selected from the group consisting of aziridinyl, azetidinyl, pyrrolidinyl, piperidino, hexahydroazepinyl, heptamethylenimino, octamethylenimino, morpholino and 4-lower-alkyl-piperazinyl, each of said hetrocyclic moieties having attached as substituents on

the carbon atoms thereof 0-3 lower alkyl groups, hydroxy or alkoxy, and wherein R_2 is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkoxyalkyl, lower cycloalkyl, lower aryl, lower aralkyl, lower alkaryl, lower alkoxyaralkyl, and lower haloaralkyl, and the tautomers and pharmacologically acceptable acid addition salts thereof;

(b) from about 5 to about 25 percent by weight of a hydroxyl radical scavenger selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from one to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from two to about 14 carbon atoms, and combinations thereof; and

(c) an occlusive or semiocclusive pharmaceutical carrier in which said 1,2-dihydro-1-hydroxypyrimidine compound and said hydroxyl radical scavenger are substantially homogenously dispersed, said carrier selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions.

34. The method of claim 33, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is minoxidil.

35. The method of claim 33, wherein said 1,2-dihydro-1-hydroxypyrimidine compound is present in an amount of about 2 percent by weight of the composition.

36. The method of claim 33, wherein said hydroxyl radical scavenger is present in an amount of from about 15 to about 20 percent by weight of the composition.

37. The method of claim 33, wherein said hydroxyl radical scavenger is dimethyl sulfoxide.

38. The method of claim 33, wherein said composition further comprises from about 0.01 to about 5 percent by weight of an antiandrogen selected from the group consisting of: spironolactone, cyproterone, and cyproterone acetate.

39. The method of claim 38, wherein said antiandrogen is spironolactone.

40. The method of claim 39, wherein said spironolactone is present in an amount of about 0.01 percent by weight.

41. The method of claim 38, wherein said antiandrogen is cyproterone.

42. The method of claim 41, wherein said cyproterone is present in an amount of about 0.1 percent by weight.

43. The method of claim 38, wherein said antiandrogen is cyproterone acetate.

44. The method of claim 43, wherein said cyproterone acetate is present in an amount of about 0.1 percent by weight.

45. The method of claim 33, further comprising water soaking said skin just prior to said application of said composition.

46. The method of claim 33, wherein about 0.5 ml of said composition is applied to the skin once a day.

47. The method of claim 33, wherein said composition is applied to the scalp.

48. A method of stimulating hair growth comprising:

water-soaking the scalp; and

once a day, applying to said water-soaked scalp about 0.5 ml of a composition comprising:

(a) about 2 percent by weight of minoxidil;

(b) from about 15 to about 20 percent by weight of dimethyl sulfoxide; and

(c) an occlusive or semiocclusive pharmaceutical carrier in which said minoxidil and said dimethyl sulfoxide are substantially homogenously dispersed, said carrier being an oil-in-water emulsion.

49. The method of claim 48, wherein said composition further comprises:

(d) about 0.01 weight percent spironolactone substantially homogenously dispersed in said carrier.

50. A vehicle for topical application of minoxidil to stimulate hair growth, consisting essentially of:

(a) an emulsion of oil and water; and

(b) substantially homogenously dispersed therein a pharmaceutically acceptable hydroxyl radical scavenger in a proportion which is synergistically effective to stimulate hair growth when the minoxidil is dispersed in the vehicle in a proportion of 2 percent by weight.

51. The vehicle of claim 50, wherein said emulsion is an oil-in-water emulsion.

52. The vehicle of claim 50, wherein said emulsion is a water-in-oil emulsion.

53. The vehicle of claim 50, wherein said hydroxyl radical scavenger is selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from 1 to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from 2 to about 14 carbon atoms, and combinations thereof.

54. The vehicle of claim 50, wherein said hydroxyl radical scavenger is present in an amount of from about 5 to about 25 percent by weight of the vehicle.

55. The vehicle of claim 50, further consisting essentially of an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

56. The vehicle of claim 55, wherein said antiandrogen is present in an amount of from about 0.01 to about 5 percent by weight of the vehicle.

57. The vehicle of claim 56, wherein said antiandrogen is selected from the group consisting of: spironolactone, cyproterone, cyproterone acetate and combinations thereof.

58. A vehicle for topical application of hair growth stimulants, consisting essentially of:

(a) an emulsion selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions; and

(b) substantially homogenously dispersed therein from about 5 to about 25 percent by weight of the vehicle of a sulfoxide selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from 1 to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from 2 to about 14 carbon atoms, and combinations thereof.

59. The vehicle of claim 58, wherein said sulfoxide is present in an amount of from about 15 to about 20 percent by weight of the vehicle.

60. The vehicle of claim 58, wherein said sulfoxide is dimethyl sulfoxide.

61. The vehicle of claim 58, wherein said emulsion is an oil-in-water emulsion.

62. The vehicle of claim 58, further consisting essentially of propylene glycol.

63. The vehicle of claim 58, further consisting essentially of from about 0.01 to about 5 percent by weight of an antiandrogen selected from the group consisting of: spironolactone, cyproterone, cyproterone acetate and combinations thereof.

64. The vehicle of claim 63, wherein said antiandrogen is spironolactone present in an amount of about 0.2 percent by weight.

65. The vehicle of claim 63, wherein said antiandrogen is cyproterone present in an amount of about 0.1 percent by weight.

66. The vehicle of claim 63, wherein said antiandrogen is cyproterone acetate present in an amount of about 0.1 percent by weight.

67. A vehicle for topical application of hair growth stimulants, consisting essentially of:

(a) an oil-in-water emulsion; and

(b) from about 15 to about 20 percent by weight of dimethyl sulfoxide substantially homogenously dispersed therein.

68. In a method of stimulating hair growth comprising topically applying a hair growth stimulant in association with a pharmaceutical carrier to the skin, the improvement wherein the pharmaceutical carrier is a vehicle consisting essentially of:

(a) an emulsion of oil and water; and

(b) substantially homogenously dispersed therein a pharmaceutically acceptable hydroxyl radical scavenger in a proportion which is synergistically effective to stimulate hair growth when the topical hair growth stimulant is dispersed in the vehicle.

69. The improvement of claim 68, wherein said emulsion is an oil-in-water emulsion.

70. The improvement of claim 68, wherein said emulsion is a water-in-oil emulsion.

71. The improvement of claim 68, wherein said hydroxyl radical scavenger is selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from 1 to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from 2 to about 14 carbon atoms, and combinations thereof.

72. The improvement of claim 68, wherein said hydroxyl radical scavenger is present in an amount of from about 5 to about 25 percent by weight of the vehicle.

73. The improvement of claim 68, wherein said proportion of said hydroxyl radical scavenger is synergistically effective when the hair growth stimulant is minoxidil present in an amount of about 2 percent by weight of said vehicle.

74. The improvement of claim 68, wherein the vehicle further consists essentially of an antiandrogen which interferes with the binding of dihydrotestosterone to receptors.

75. The improvement of claim 74, wherein said antiandrogen is present in an amount of from about 0.01 to about 5 percent by weight of the vehicle.

76. The improvement of claim 74, wherein said antiandrogen is selected from the group consisting of: spironolactone, cyproterone, cyproterone acetate and combinations thereof.

77. In a method of stimulating hair growth comprising topically applying a hair growth stimulant in association with a pharmaceutical carrier to the skin, the improvement wherein the carrier is a vehicle consisting essentially of:

(a) an emulsion selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions; and

(b) substantially homogenously dispersed therein from about 5 to about 25 percent by weight of the vehicle of a sulfoxide selected from the group consisting of: alkyl methyl sulfoxides in which the alkyl substituent has from 1 to about 14 carbon atoms, β-hydroxyalkyl methyl sulfoxides in which the hydroxyalkyl substituent has from 2 to about 14 carbon atoms, and combinations thereof.

78. The improvement of claim 77, wherein said sulfoxide is present in an amount of from about 15 to about 20 percent by weight of the vehicle.

79. The improvement of claim 77, wherein said sulfoxide is dimethyl sulfoxide.

80. The improvement of claim 77, wherein said emulsion is an oil-in-water emulsion.

81. The improvement of claim 77, wherein the vehicle further consists essentially of propylene glycol.

82. The improvement of claim 77, wherein the vehicle further consists essentially of from about 0.01 to about 5 percent by weight of an antiandrogen selected from the group consisting of: spironolactone, cyproterone, cyproterone acetate and combinations thereof.

83. The improvement of claim 82, wherein said antiandrogen is spironolactone present in an amount of about 0.2 percent by weight.

84. The improvement of claim 82, wherein said antiandrogen is cyproterone present in an amount of about 0.1 percent by weight.

85. The improvement of claim 82, wherein said antiandrogen is cyproterone acetate present in an amount of about 0.1 percent by weight.

86. In a method of stimulating hair growth comprising topically applying minoxidil in association with a pharmaceutical carrier to the skin, the improvement wherein the carrier is a vehicle consisting essentially of:

(a) an oil-in-water emulsion; and

(b) from about 15 to about 20 percent by weight of dimethyl sulfoxide substantially homogenously dispersed therein.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/01393

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT. CL.[4]: A61K 7/06
U.S. CL. : 424/70

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/70

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	U.S.,A, 3,551,554, (HERSCHLER), 12 December 1970, Column 8, lines 54 to 56 and Column 14, lines 14 to 25.	4,5,6,7 to 9,15, to 21, and 23
A	U.S.,A, 3,896,238, (SMITH) 22 July 1975, Column 18, lines 1 to 10	4,5,6 to 9, 15 to 21 and 23
X	U.S.,A, 4,139,619, (CHIDSEY), 02 February, 1979, Column 4, lines 38 to 60	1 to 3, 10 to 14, 22 and 24 to 86
A	U.S.,A, 4,367,227, (BINGHAM), 04 January 1983, Column 2, lines 1 to 9	4,5,6 to 9,15 to 21 and 23

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
09 September 1986	17 SEP 1986
International Searching Authority [1]	Signature of Authorized Officer [20]
ISA/US	Dale R. Ore Dale R. Ore